

Original research

Corticosteroid therapy for treating acute exacerbation of interstitial lung diseases: a systematic review

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ABSTRACT

Introduction Acute exacerbation of interstitial lung disease (AE-ILD) often results in death and poses significant challenges in clinical management. While corticosteroids are frequently employed, the optimal regimen and their clinical efficacy remain uncertain. To address this knowledge gap, we undertook a systematic review to evaluate the impact of steroid therapy on clinical outcomes in patients experiencing AE-ILD.

Method Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, we systematically searched multiple databases, identifying 12 454 articles. After removing duplicates and screening titles and abstracts, 447 articles were selected for full-text review. Ultimately, nine studies met inclusion criteria, comparing high-dose corticosteroids with low-dose or non-steroidal interventions in treating AE-ILD. Key outcomes included in-hospital and long-term mortality, as well as AE recurrence.

Results Analysis of nine studies (total n=18 509) revealed differential treatment effects based on the ILD subtype. In non-idiopathic pulmonary fibrosis (IPF) ILD, high-dose corticosteroid therapy (>1.0 mg/kg prednisolone) demonstrated improved survival (adjusted HR 0.221, 95% CI 0.102 to 0.480, p<0.001) and reduced 90-day mortality. Early tapering of high-dose corticosteroids (>10% reduction within 2 weeks) reduced in-hospital mortality (adjusted HR 0.37, 95% CI 0.14 to 0.99). Higher cumulative doses in the first 30 days (5185±2414 mg/month vs 3133±1990 mg/month) were associated with lower recurrence rates (adjusted HR 0.61, 95% CI 0.41 to 0.90, p=0.02). In IPF patients, however, high-dose therapy showed inconsistent benefits, with some studies reporting increased mortality risk (OR 1.075, 95% CI 1.044 to 1.107, p<0.001).

Conclusion This review emphasises the potential benefits of individualised treatment approaches for AE-ILD but highlights the need for caution in making definitive recommendations. Although high-dose corticosteroids may show promise, particularly in non-IPF cases, the current evidence is inconsistent, and the lack of robust supporting literature makes it difficult to draw firm conclusions. Further research through randomised controlled trials is necessary to refine and optimise therapeutic strategies for AE-ILD.

INTRODUCTION

Interstitial lung diseases (ILDs) encompass a heterogeneous group of disorders characterised by inflammation and fibrosis of the lung parenchyma, including idiopathic pulmonary fibrosis (IPF), connective tissue disease-associated ILD

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Corticosteroids are widely used for acute exacerbation of interstitial lung disease (AE-ILD), but optimal dosing and duration remain controversial with varying practices across healthcare settings.

WHAT THIS STUDY ADDS

⇒ Higher-dose corticosteroids may improve survival specifically in non-idiopathic pulmonary fibrosis (IPF) ILD patients, and early tapering may reduce in-hospital mortality, while higher initial doses may reduce recurrent exacerbations.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This review supports tailoring corticosteroid therapy based on the ILD subtype (particularly IPF vs non-IPF) and incorporating early tapering strategies while highlighting the critical need for standardised definitions and outcome measures in future research.

(CTD-ILD), and others.¹ These conditions often lead to respiratory decline and acute exacerbation of ILD (AE-ILD), which can result in respiratory failure and death.^{2–7}

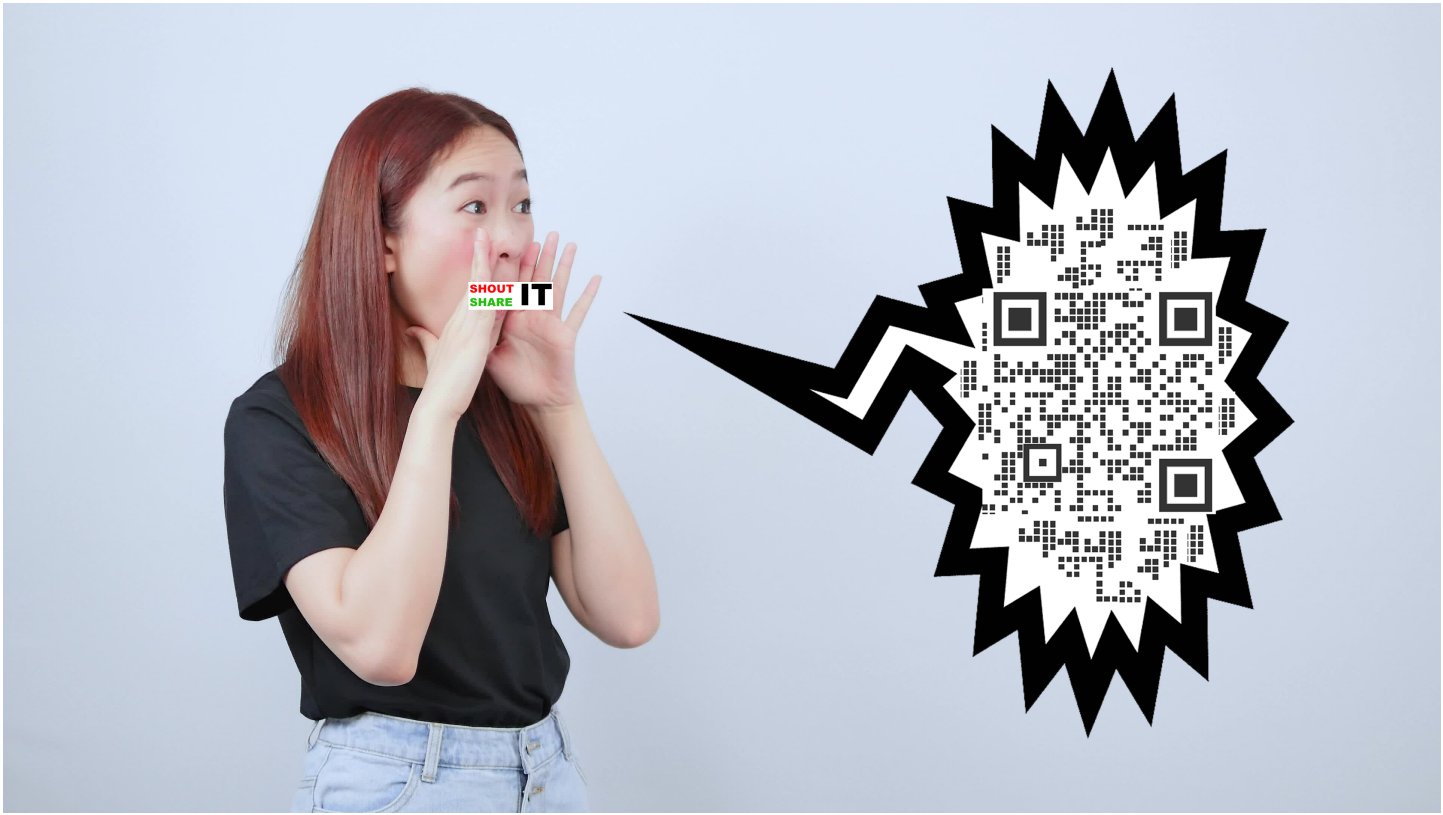
Corticosteroids are frequently employed in managing AE-ILD, with varying doses and durations.⁸ These medications aim to alleviate inflammation, reduce lung injury and improve gas exchange.⁹ However, the optimal dosage and duration of corticosteroid therapy remain controversial due to potential adverse effects,¹⁰ including infections, gastrointestinal bleeding and steroid-induced diabetes. Moreover, Leuschner *et al*¹¹ observed significant disparities in the definitions and therapeutic strategies employed for AE-ILD. Considering the lack of standardised protocols, further investigations are essential to refine management approaches and enhance patient outcomes.¹²

In recent years, there has been growing interest in elucidating the effectiveness and safety profiles of different corticosteroid therapy regimens in managing AE-ILD, as practices vary across healthcare settings.^{13–21} Dosing regimens range from 0.5 mg/kg/day to 1000 mg/day of methylprednisolone, treatment durations span from 3 days to several weeks, tapering protocols vary widely between institutions, and combination therapy approaches lack standardisation. These inconsistencies emphasise



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the need for further research to identify the most effective and consistent treatment strategies. Understanding the comparative efficacy of high versus low-dose corticosteroid therapy, as well as the impact of treatment duration and tapering protocols, is crucial for optimising patient outcomes and minimising complications.

This systematic review aims to evaluate the effectiveness of different corticosteroid therapy regimens in ameliorating outcomes among patients experiencing AE-ILD, focusing on survival time, rehospitalisation within 30 days, recurrence of AE and mortality rates. Our findings aim to inform clinical practice and guide future research directions in this critical area of ILD management.

METHOD

Search strategy

Two investigators, NS and FDG, independently conducted a systematic literature search across multiple databases, including Medline, Embase, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, spanning from each database's inception to August 2024. The objective of this search was to identify published studies that inform the efficacy of steroid therapy regimens in ameliorating outcomes among patients experiencing AE-ILD, focusing on parameters including survival rate, hospitalisation frequency, recurrences of AE-ILD and mortality rates. The search strategy encompassed the utilisation of the following terms: "interstitial lung disease," "ILD," "Idiopathic pulmonary fibrosis," "IPF," "lung fibrosis," "fibrosing alveolitis," "Connective tissue disease-associated ILD," "CTD-ILD," "pulmonary pneumonitis," "pulmonary eosinophilia pneumonia," "Nonspecific interstitial pneumonia," "NSIP," "Cryptogenic organizing pneumonia," "COP," "Hypersensitivity pneumonitis," "Drug-induced ILD" combined with "adrenal cortex hormone," "steroid," "steroids," "glucocorticoid," "corticoid," "corticosteroid," "beclomethasone," "betamethasone," "fluticasone," "cortisone," "dexamethasone," "hydrocortisone," "prednisolone," "prednisone," "methylprednisolone," "triamcinolone," in addition to terms signifying exacerbation such as "exacerbation," "disease exacerbation," "flare" and "flare up," as detailed in the supplementary data (see online supplemental file 1). Furthermore, the investigators manually examined the reference lists of selected articles for potentially pertinent studies based on inclusion criteria as described below without imposing any language restrictions. The systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement standards,²² and the study protocol was registered in the PROSPERO International prospective register of systematic reviews under the ID CRD 42024537706.

INCLUSION AND EXCLUSION CRITERIA

For inclusion in the review, studies were required to be clinical trials or observational studies, comprising cross-sectional, case-control or cohort designs, examining the efficacy of high-dose steroid therapy in improving outcomes for patients experiencing AE-ILD. These studies must have included a control group receiving either low-dose corticosteroid treatment or non-corticosteroid interventions compared with those administered high-dose corticosteroids (various definitions). The eligibility assessment of retrieved articles was conducted independently by NS and FDG, with any disparities resolved by discussion with reference to the primary studies. The quality of each study was also independently evaluated by the investigators using the

Newcastle-Ottawa Quality Scale, which assesses studies across three domains: selection of participants (S), comparability between study groups (C) and ascertainment of exposure (for case-control studies) or outcome (for cohort studies) (O). Studies achieving a Newcastle-Ottawa Scale score of six or higher were considered good methodological quality.

Studies were excluded based on the following criteria: non-comparative studies, studies lacking clear corticosteroid dosing information, studies without defined outcomes, and case reports or case series. These exclusions ensured that only studies with robust, comparable data and relevant outcomes were included in the final review.

DATA EXTRACTION

Data were extracted using a standardised form, capturing information on the article title, primary author, publication year, country, type of corticosteroid intervention (high-dose vs low-dose or non-corticosteroid), outcome measures (including survival time, recurrence of AE-ILD, rehospitalisation within 30 days and mortality rates (in-hospital, 28 days, 90 days, 1 year)), sample sizes, demographics and adjusted confounders with effect estimates and 95% CIs, as detailed in the tables. Data extraction was performed independently by NS and FDG., with discrepancies resolved by referencing the primary studies.

RESULTS

Our systematic review process involved a thorough evaluation of 12454 potentially relevant articles, from which 195 duplicates were initially removed, leaving 12259 unique studies for title and abstract screening. Through rigorous application of inclusion criteria focusing on article type, study design, population and outcomes, 11812 studies were excluded at the screening stage. Of the remaining 447 articles that underwent full-text review, 438 were ultimately excluded, with 249 articles eliminated due to inappropriate study designs (including narrative reviews, conference abstracts, case reports and non-clinical studies) and 189 articles removed for inadequate outcome reporting (such as incomplete data, surrogate endpoints or insufficient follow-up periods). The final selection comprised nine high-quality observational studies, including both cohort and case-control designs, which collectively analysed data from 18509 patients. [Figure 1](#) outlines our search methodology and selection process.

Types of interstitial lung disease (ILDs)

As detailed in [table 1](#), four studies included all ILD subtypes,^{14 15 19 21} while the remaining five^{13 16–18 20} involved only IPF. Arai *et al*¹⁴ adhered to the guidelines outlined by the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association, complemented by high-resolution computed tomography (HRCT). Jang *et al*¹⁹ used a multidisciplinary approach involving comprehensive evaluations of patient history, physical examination, HRCT scans and histopathological findings. Yamazaki *et al*²⁰ followed the criteria established in the Investigating Nintedanib in Progressive Fibrosing Interstitial Lung Disease trial, which mandated either surgical lung biopsy or HRCT. Hyung *et al*¹⁸ employed validated lung texture analysis software (AVIEW Lung Texture V.1.1.43.7, Coreline Soft). The remaining five studies^{13 15–17 21} relied on diagnostic coding.

Definitions of interstitial lung disease (ILD) exacerbation

The definitions of ILD exacerbation varied across studies, as detailed in [table 1](#). Arai *et al*¹⁴ followed the Japanese guideline,²³

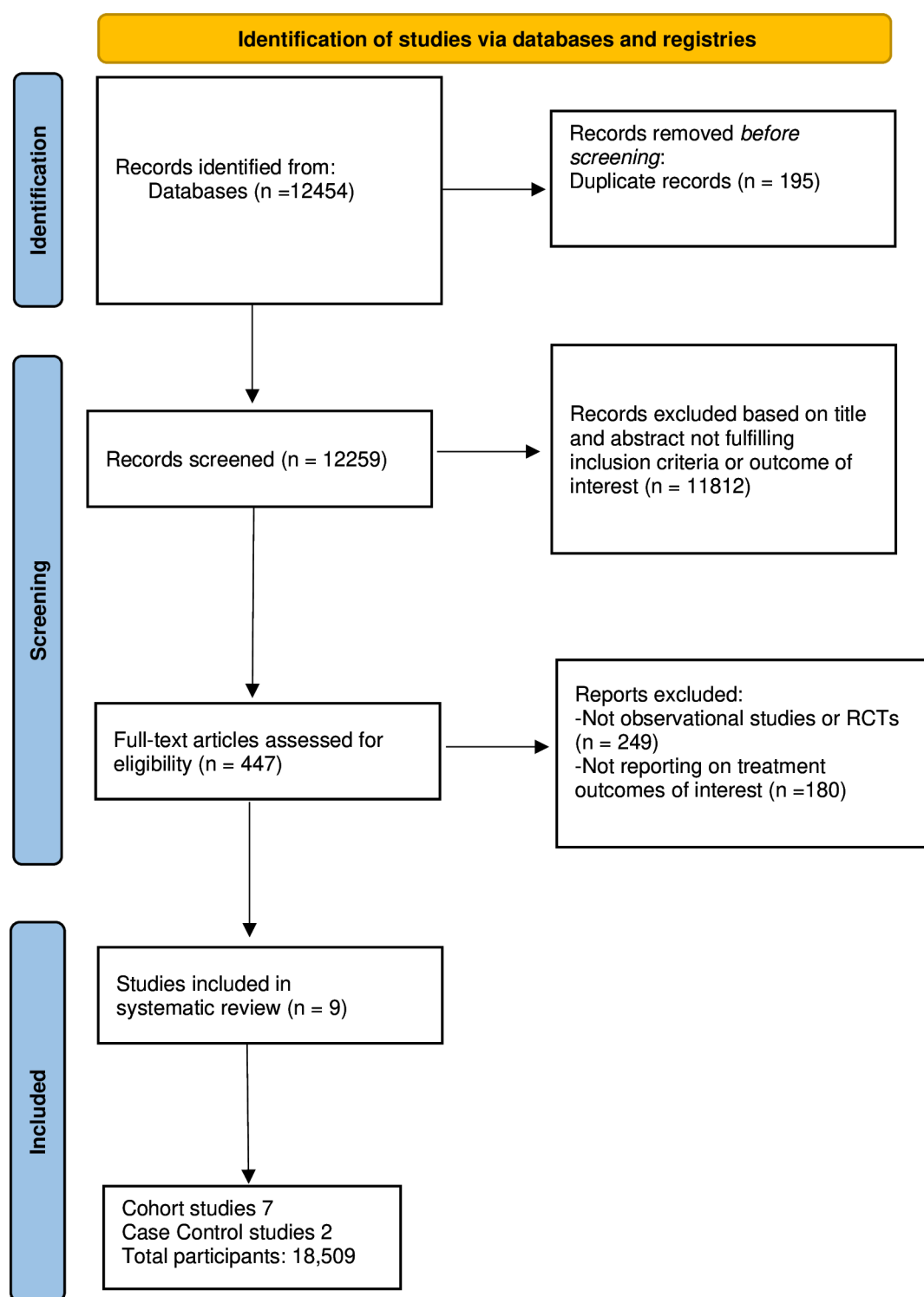


Figure 1 Literature review process. RCTs, randomised controlled trials.

defining exacerbation as worsening dyspnoea with new ground glass opacity on HRCT and a reduction in PaO₂, excluding other aetiologies. Jang *et al*¹⁹ characterised exacerbation as patients presenting to the emergency department with dyspnoea or persistent symptoms for more than 1 month, after excluding other causes. Yamazaki *et al*,²⁰ Anan *et al*¹³ and Koshy *et al*²¹ adhered to the international working group report definition.⁶ Awano *et al*¹⁵ identified exacerbation as corticosteroid administration within 4 days of admission, after excluding cardiac conditions. Cuerpo *et al*¹⁶ considered exacerbation as unexplained

worsening dyspnoea in IPF, categorising exacerbations as acute or subacute based on timing and excluding other potential aetiologies. Hyung *et al*¹⁸ described exacerbation as respiratory deterioration within 30 days with new alveolar opacities on CT. Farrand *et al*¹⁷ did not specify the definition.

Corticosteroid exposure and comparator groups

As summarised in table 2, all studies reported the use of high-dose or non-early taper dose corticosteroids, with variations in

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Table 1 Study characteristics

Study	Country	Year	Study design	ILD diagnosis	Types of ILD	ILD exacerbation Definition
Arai <i>et al</i> ¹⁴	Japan	2017	Cohort	ATS/ERS/JRS/ALAT guideline: two ILD experts and radiologist reviewed HRCT	Various types of ILD	Japanese guidelines diagnose acute IPF exacerbation by worsening dyspnoea, new ground glass opacities on HRCT and a PaO ₂ drop of over 10 mm Hg, excluding other respiratory causes.
Farrand <i>et al</i> ¹⁷	USA	2018	Cohort	Diagnostic code.	Only IPF.	The definition of ILD exacerbation was not explicitly provided.
Jang <i>et al</i> ¹⁹	Korea	2021	Cohort	Comprehensive ILD assessment: history, exam, labs, HRCT, histopathology for multidisciplinary diagnosis.	Various types of ILD.	ED presentations with dyspnoea excluded fluid overload, CHF, pulmonary embolism, non-respiratory dyspnoea and symptoms worsening over 1 month.
Yamazaki <i>et al</i> ²⁰	Japan	2021	Case control	IPF diagnosed per INPULSIS criteria; HRCT needed honeycombing, reticular abnormalities, and traction bronchiectasis, mainly in lower and outer lungs, without atypical UIP features.	Only IPF.	AE-IPF per ATS: prior/concurrent IPF, acute dyspnoea, new ground-glass opacities or UIP on CT, and exclusion of cardiac failure or fluid overload.
Awano <i>et al</i> ¹⁵	Japan	2023	Cohort	Japanese Diagnosis Procedure Combination database: Dx code for interstitial pneumonia, excluding secondary ILDs.	Various types of ILD.	Received steroid starting within 4 days after admission after exclude cardiac conditions.
Anan <i>et al</i> (multicentre cohort) ¹³	Japan	2022	Cohort	IPF diagnosis CODE. Exclusions: secondary IP, cancer, acute conditions, treatment refusal, no corticosteroids in 14 days, minimal dosage, short stays.	Only IPF.	AE-IPF diagnosis used criteria from the international working group; HRCT findings were assessed by two expert radiologists.
Anan <i>et al</i> (administrative cohort) ¹³	Japan	2022	Cohort	Diagnostic classifications: AE (worsening dyspnoea and UIP infiltrates within 30 days, IPF); SAE (dyspnoea not meeting AE criteria); AEKE (dyspnoea with identified cause within 30 days).	Only IPF.	AE-IPF diagnosis used criteria from the international working group; HRCT findings were assessed by two expert radiologists.
Cuerpo <i>et al</i> ¹⁶	Spain	2019	Case control	Dx code: IPF.	Only IPF.	Diagnostic classifications: AE (worsening dyspnoea and UIP infiltrates, IPF); SAE (dyspnoea not meeting AE criteria); AEKE (dyspnoea with identified cause).
Hyung <i>et al</i> ¹⁸	Korea	2023	Cohort	Only IPF cases were quantitatively analysed using AVIEW Lung Texture software, validated against radiologists' visual evaluation.	Only IPF.	AE-IPF was defined as acute respiratory deterioration within 30 days accompanied by newly developed alveolar opacities on chest CT.
Koshy <i>et al</i> ²¹	Australia	2024	Cohort	A code-based algorithm identified admissions with acute respiratory symptoms and FILD diagnostic codes. Two pulmonologists confirmed fibrosis using ATS criteria for HRCT patterns.	Various types of ILD (specifically fibrotic).	AE-IPF diagnosis used criteria from the international working group.

AE-IPF, acute exacerbation of idiopathic pulmonary fibrosis; AEKE, acute exacerbation with known etiology; ALAT, Latin American Thoracic Association; ATS, American Thoracic Society; CHF, congestive heart failure; Dx, diagnosis; ED, emergency department; ERS, European Respiratory Society; FILD, fibrotic interstitial lung disease; HRCT, high-resolution CT; ILD, interstitial lung disease; INPULSIS, International Study of Nintedanib in Pulmonary Fibrosis; IP, interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; JRS, Japanese Respiratory Society; PaO₂, partial pressure of oxygen; SAE, subacute exacerbation; UIP, usual interstitial pneumonia.

dosage, compared with low-dose, no or early taper dose corticosteroids. Arai *et al*¹⁴ defined a high dose as a 1 g pulse for 3 days followed by prednisolone ≥ 0.60 mg/kg versus <0.60 mg/kg. Farrand *et al*¹⁷ characterised high doses as receiving methylprednisolone ≥ 500 mg/day or high-dose prednisolone (≥ 0.5 mg/kg) for 2 days or more, compared with no corticosteroids. Jang *et al*¹⁹ defined high dose as receiving prednisolone >1.0 mg/kg versus 0 to 1.0 mg/kg. Awano *et al*¹⁵ identified high doses as receiving 500–1000 mg/day of intravenous methylprednisolone for 3 days, compared with 100–200 mg/day of intravenous methylprednisolone for at least 5 days. Cuerpo *et al*¹⁶ did not define high-dose corticosteroids but distinguished between high dose and low dose by setting 55 mg/day of prednisolone as the cut-off. Hyung *et al*¹⁸ defined a high dose as a pulse dose of corticosteroids (≥ 250 mg/day of methylprednisolone or equivalent) within 7 days of hospital admission, compared with a non-pulse regimen typically involving 1 mg/kg/day of methylprednisolone.

Yamazaki *et al*²⁰ compared high and low-dose regimens without specific definition; instead, they calculated the accumulated corticosteroid dosing over a specific period, compared

with those without. Anan *et al*¹³ compared early tapering of corticosteroids, defining early tapering as a reduction of the maintenance dose by more than 10% within 2 weeks of admission versus non-early tapering, where the reduction was less than 10%. Koshy *et al*²¹ defined corticosteroid treatment as receiving at least 0.5 mg/kg/day of prednisolone-equivalent for a minimum of 3 days within the first 72 hours of admission, comparing this group to a control group that did not receive corticosteroids during the same period.

TREATMENT OUTCOMES

The included studies yielded insights into various outcomes. First, five studies^{14 17–19 21} reported survival time. Second, concerning mortality risk, six studies^{13 15–18 21} documented the risk of in-hospital mortality, with one study¹⁵ assessing mortality risk after 28 days. Additionally, three studies^{13 18 19} examined mortality risk at 90 days, and two studies^{16 18} investigated the mortality risk at 1 year. Third, rehospitalisation was addressed by two studies,^{17 21} which reported the risk of rehospitalisation

Table 2 Type and dose/duration of corticosteroid treatment and quality assessment

Study	Type of steroid	Definition of high dose	Definition of low dose/ none	Definition of non-early taper dose of steroid	Definition of early taper dose of steroid	Confounder adjustment for prevalence	Quality assessment
Arai <i>et al</i> ¹⁴	Methylprednisolone/prednisolone	1 g pulse of methylprednisolone intravenous for 3 days, followed by prednisolone at a dosage of ≥ 0.60 mg/kg	1 g pulse of methylprednisolone intravenous for 3 days, then prednisolone at a dosage of less than 0.60 mg/kg	Not reported	Not reported	LTOT pre-AE and lower immunoglobulin G at diagnosis	S4, C2, O3
Farrand <i>et al</i> ¹⁷	Methylprednisolone/prednisolone	Methylprednisolone intravenous pulse of at least 500 mg/day or high-dose prednisolone (at least 0.5 mg/kg) for 2 days or more	No steroid	Not reported	Not reported	Initial admission location, baseline oxygen use, do-not-resuscitate order, BMI and antibiotic therapy. ICU admission and mechanical ventilation are considered time-dependent covariates	S4, C2, O3
Jang <i>et al</i> ¹⁹	Prednisolone	Prednisolone >1.0 mg/kg	Prednisolone 0 to 1.0 mg/kg	Not reported	Not reported	Corticosteroid dose, initial P/F ratio and mechanical ventilation within 3 days	S4, C2, O3
Yamazaki <i>et al</i> ²⁰	Prednisolone	Not reported	Not reported	Not reported	Not reported	Total corticosteroid doses (mg/month) over days 61 to 90, along with sex, age, BMI and antifibrotic agent use at discharge	S4, C2, O3
Awano <i>et al</i> ¹⁵	Methylprednisolone/prednisolone	500–1000 mg/day of intravenous methylprednisolone for 3 days	100–200 mg/day of intravenous methylprednisolone for at least 5 days	Not reported	Not reported	Sex, age, BMI, dyspnoea score, comorbidity index, smoking index, Barthel index, hospitalisation history, academic status, unscheduled admissions, ICU admissions, and AE-IIPs drugs	S4, C2, O3
Anan <i>et al</i> (multicentre cohort) ¹³	Prednisolone	Not reported	Not reported	1 g/day for 3 days with no early tapering	1 g/day for 3 days, then corticosteroid maintenance dose reduced by over 10% within 2 weeks of admission	Age, sex, LDH, CRP, albumin, KL-6, CCI, LTOT before AE, PaO ₂ /FiO ₂ , SpO ₂ /FiO ₂ on day 7, HRCT score, imaging changes, pre-admission steroid and immunosuppressant use, and initial steroid dose	S4, C2, O3
Anan <i>et al</i> (administrative cohort) ¹³	Prednisolone	Not reported	Not reported	1 g/day for 3 days with no early tapering	1 g/day for 3 days, then corticosteroid maintenance dose reduced by over 10% within 2 weeks of admission	Age, sex, LDH, CRP, albumin, KL-6, CCI, LTOT before AE, PaO ₂ /FiO ₂ , SpO ₂ /FiO ₂ on day 7, HRCT score, imaging changes, pre-admission steroid and immunosuppressant use, and initial steroid dose	S4, C2, O3
Cuerpo <i>et al</i> ¹⁶	Prednisolone	Not defined. But documented ≥ 55 mg/day	Not defined. But documented < 55 mg/day	Not reported	Not reported	Age, gender, FVC, PaFiO ₂ before exacerbation, daily corticosteroid dose and antibiotic therapy during hospitalisation	S4, C2, O3
Hyung <i>et al</i> ¹⁸	Methylprednisolone	A pulse dose of corticosteroids (≥ 250 mg/day of methylprednisolone intravenous or equivalent) within 7 days of hospitalisation	Patients who did not receive a pulse dose of corticosteroids (usually treated with 1 mg/kg/day of methylprednisolone)	Not reported	Not reported	Age, sex, BMI, lung cancer history, WBC count, CRP level, respiratory support, quantitative chest CT data	S4, C2, O3
Koshy <i>et al</i> ²¹	Prednisolone	Received corticosteroid treatment within the first 72 hours of admission	Did not receive early corticosteroid treatment	Not reported	Not reported	Age, CCI, lung function by FVC, severity by oxygen requirement at admission	S4, C2, O3

AE, acute exacerbation; AE-IIP, acute exacerbation of idiopathic interstitial pneumonia; BMI, body mass index; C, case; CCI, Charlson Comorbidity Index; CRP, C-reactive protein; FiO₂, fraction of inspired oxygen; FVC, forced vital capacity; HRCT, high-resolution CT; ICU, intensive care unit; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; LTOT, long-term oxygen therapy; O, outcome; PaO₂, partial pressure of oxygen; P/F ratio, PaO₂/FiO₂ ratio; S, study; SpO₂, peripheral capillary oxygen saturation; WBC, white blood cell.

within 30 days. Finally, the risk of recurrent exacerbation was discussed in one study.²⁰

PATIENT CHARACTERISTICS

Tables 3 and 4 provide an overview of participant characteristics from the included studies, suggesting a diverse range of demographics, smoking history, cancer prevalence and comorbidity burden. Sample sizes varied from 50 participants in Cuerpo *et*

*al*¹⁶ to a large cohort of 17317 individuals by Awano *et al*.¹⁵ Most studies included a majority of male participants, except for Farrand *et al*.¹⁷ Cancer prevalence, particularly lung cancer, was reported in several studies. Smoking history, including the number of pack years, was provided in some studies. The Charlson Comorbidity Index (CCI) was used in three studies to assess comorbidity burden. Farrand *et al*¹⁷ found no significant difference between the corticosteroid and no corticosteroid

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Table 3 Participant characteristics

Study	Sample size (n)		Sex (female, %)		Age, years (range)	
	High/non-early taper dose	Low dose/none/early taper	High/non-early taper dose	Low dose/none/early taper	High/non-early taper dose	Low dose/none/early taper
Arai <i>et al</i> ¹⁴	67	18	19	17	72 (65–76)	69 (66–76)
Farrand <i>et al</i> ¹⁷	37	45	57	51	67 (56–77)	67 (57–77)
Jang <i>et al</i> ¹⁹	Total cohort: 185		Total cohort: 33		Total cohort: 69 (57–80)	
Yamazaki <i>et al</i> ²⁰	63 (9 with recurrent exacerbation, 54 non-recurrent)		21 (0 with recurrent exacerbation, 24 non-recurrent)		75 (75, recurrent exacerbation, 75, non-recurrent)	
Awano <i>et al</i> ¹⁵	16 998	319	29.9	29.2	≥ 80, 30.4%	≥ 80, 37.9 %
Anan <i>et al</i> (multicentre cohort) ¹³	87	66	20	35	78 (71–82)	78 (73–84)
Anan <i>et al</i> (administrative cohort) ¹³	87	142	22	35	78 (72–82)	77 (70–82)
Cuerpo <i>et al</i> ¹⁶	Total 50		Total 32		Total 75	
Hyung <i>et al</i> ¹⁸	59	179	25	25	73 (68–79)	72 (67–77)
Koshy <i>et al</i> ²¹	46	61	48	38	67.4 (65.6–69.2)	73.0 (71.7–74.3)

groups, whereas Awano *et al*¹⁵ reported a higher comorbidity burden in the corticosteroid group. Koshy *et al*²¹ observed a mean CCI of 3.6 ± 0.3 for the corticosteroid group and 4.8 ± 0.3 for the no corticosteroid group, with a statistically significant difference ($p < 0.05$), indicating a greater comorbidity burden in the no corticosteroid group. However, reported comorbidities such as cardiac disease varied among studies, suggesting differences in the health status and medical history.

TREATMENT OUTCOME MEASURES

Table 5 summarises the outcomes, which are described below.

Survival time

Arai *et al*¹⁴ analysed 85 patients with acute exacerbation of idiopathic interstitial pneumonia (AE-IIP) to identify factors influencing survival. They found a median survival of 49 days for all AE-IIP patients, with no significant difference between AE-IPF and AE-non-IPF cases. A significant prognostic factor for favourable outcomes in AE-IIPs was an initial prednisolone dose

≥ 0.6 mg/kg, particularly in patients not managed with positive pressure ventilation.

Farrand *et al*¹⁷ included 82 IPF patients and found no significant survival benefit from corticosteroids, which may increase mortality (adjusted HR of 6.17).

Two Korean studies reported survival outcomes. Jang *et al*¹⁹ studied 85 patients with AE-ILD and found significantly higher survival rates with prednisolone doses exceeding 1 mg/kg in the overall AE-ILD patients, particularly in non-IPF ILD. However, 90-day mortality differences for the IPF group were not statistically significant. Hyung *et al*¹⁸ analysed 59 participants with AE-IPF who received pulse-dose corticosteroids compared with those who did not, finding no significant difference in survival ($p = 0.846$).

Koshy *et al*²¹ conducted a study involving 107 patients with fibrotic ILDs. Of these, 46 patients received corticosteroid treatment (≥ 0.5 mg/kg/day of prednisolone equivalent within the first 3 days). The corticosteroid group had a median survival of 221 days compared with 520.5 days in the non-corticosteroid group.

Table 4 Participant characteristics

Study	Cancer (%)		Smoking (current and ex-smoker, %)		CCI	
	High/non-early taper dose	Low dose/none/early taper	High/non-early taper dose	Low dose/none/early taper	High/non-early taper dose	Low dose/none/early taper
Arai <i>et al</i> ¹⁴	Not reported	Not reported	76.1	88.9	Not reported	
Farrand <i>et al</i> ¹⁷	Not reported	Not reported	Not reported	Not reported	1 (0 to 1)	0 (0–2)
Jang <i>et al</i> ¹⁹	Not reported		Total cohort: 45.4		Not reported	
Yamazaki <i>et al</i> ²⁰	Not reported		77.8 (88.9 with recurrent exacerbation, 75.9 non-recurrent)		Not reported	
Awano <i>et al</i> ¹⁵	Lung 11.9 Other types 9.5	Lung 12.9 Other types 8.2	Packs year 0 44.9% 1–39 19.2% ≥40 230.8% Missing 12.1%	Packs year 0 45.1% 1–39 16.3% ≥40 280.2% Missing 10.3%	0 :52.0% 1 :13.0% 2 :21.5% ≥3 :13.5%	0:35.7% 1:30.7% 2:17.6% ≥3:16.0%
Anan <i>et al</i> (multicentre cohort) ¹³	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Anan <i>et al</i> (administrative cohort) ¹³	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Cuerpo <i>et al</i> ¹⁶	Not reported		Total 62		Not reported	
Hyung <i>et al</i> ¹⁸	Lung cancer 8.5	Lung cancer 10.1	77.8	69.5	Not reported	Not reported
Koshy <i>et al</i> ²¹	Not reported	Not reported	55	41	3.6 (3.3 to 3.9)	4.8 (4.5–5.1)

CCI, Charlson Comorbidity Index

Table 5 Treatment outcomes

Study	Survival time	Subgroup only in non-PPV group	Hospital mortality	28-day mortality	Day mortality	1-year mortality rate	30-day rehospitalisation	Recurrent exacerbation
Arai <i>et al</i> ¹³	Survival was similar between high-dose and low-dose PSL-treated AE-IIPs (p=0.820)	High-dose PSL post-intravenous methylprednisolone improved survival in non-PPV AE-IIPs	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Farrand <i>et al</i> ¹⁷	Kaplan–Meier and Cox models: HR 3.12 (95% CI 1.68 to 5.80; p<0.001) and HR 6.17 (95% CI 1.35 to 28.14; p=0.019)	Not reported	Unadjusted HR 2.67 (0.74–9.64), p=0.13; adjusted HR 1.52 (0.37–6.18), p=0.56; weighted HR 1.31 (0.26–6.55), p=0.74	Not reported	Not reported	Not reported	Adjusted HR: 1.81 (0.46–7.17), p=0.40	Not reported
Jang <i>et al</i> ¹⁹	Higher prednisolone doses improved survival in AE-ILD and non-IPF ILD (p<0.01) but not IPF (p=0.142)	Not reported	Not reported	Not reported	Unadjusted HR: 0.38 (p=0.005) Adjusted HR: 0.22 (p<0.001)	Not reported	Not reported	Not reported
Yamazaki <i>et al</i> ²⁰	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Adjusted HR (1–30 days): 0.61 (p=0.02). Corticosteroids: 5185 mg versus 3133 mg/month (p=0.02). No differences after 30 days
Awano <i>et al</i> ¹⁵	Not reported	Not reported	Unadjusted: HR 0.87 (p=0.25). Propensity score weighted: HR 0.86 (p=0.33)	Unadjusted: HR 0.79 (p=0.066). Propensity score weighted: HR 0.88 (p=0.46)	Unadjusted HR: 0.41 (0.22–0.76) Adjusted HR: 0.37 (0.14–0.99)	Not reported	Not reported	Not reported
Anan <i>et al</i> (multicentre cohort) ¹³	Not reported	Not reported	Unadjusted: HR 0.41 Adjusted: HR 0.37	Not reported	Unadjusted HR: 0.41 (0.22–0.76) Adjusted HR: 0.37 (0.14–0.99)	Not reported	Not reported	Not reported
Anan <i>et al</i> (administrative cohort) ¹³	Not reported	Not reported	Unadjusted: HR 0.65 Adjusted: HR 0.27	Not reported	Unadjusted HR: 0.65 (0.36–1.18) Adjusted HR: 0.27 (0.094–0.83)	Not reported	Not reported	Not reported
Cuerpo <i>et al</i> ¹⁶	Not reported	Not reported	Higher corticosteroid doses increased in-hospital mortality (OR 1.044, p=0.024)	Not reported	Not reported	OR 1.075 (1.044–1.107), p<0.001	Not reported	Not reported
Hyung <i>et al</i> ¹⁸	Time to death did not differ between matched pulse and no-pulse groups (p=0.846)	Not reported	Pulse group: 11/46 (18.6%) Non-pulse group: 65/179 (36.3%) P value: 0.018	Not reported	Unadjusted HR: 0.64 (p=0.072). Adjusted HR: 0.82 (p=0.456). Matched: unadjusted HR: 0.97 (p=0.907). Adjusted HR: 1.13 (p=0.698)	Unadjusted HR: 0.75 (p=0.130). Adjusted HR: 0.89 (p=0.580). Matched: unadjusted HR: 1.01 (p=0.960). Adjusted HR: 1.08 (p=0.750)	Not reported	Not reported
Koshya <i>et al</i> ²¹	Adjusted HR for all-cause mortality: 3.25 (95% CI 1.56 to 6.77, p<0.01) HR for non-IPF versus IPF patients on steroids: 0.21 (95% CI 0.04 to 0.96, p=0.04)	Not reported	Adjusted OR: 4.11 (95% CI 1.00 to 16.83, p=0.049) (combined in-hospital mortality or lung transplantation within admission)	Not reported	Not reported	Not reported	OR: 1.94 (95% CI 0.41 to 9.13, p=0.40)	Not reported

AE-IIPs, Acute Exacerbation of Idiopathic Pulmonary Interstitial Pneumonia; AE-ILD, acute exacerbation of interstitial lung disease; IPF, idiopathic pulmonary fibrosis; PPV, positive pressure ventilation; PSL, prednisolone.

The adjusted HR for all-cause mortality was 3.25 (95% CI 1.56 to 6.77, p<0.01), indicating higher mortality in the corticosteroid group. However, non-IPF patients receiving corticosteroids had a lower risk of mortality compared with IPF patients, with a HR of 0.21 (95% CI 0.04 to 0.96, p=0.04).

In-hospital mortality

In-hospital mortality rates varied. Anan *et al*¹³ conducted an extensive study involving two Japanese cohorts. The first

consisted of patients from eight Japanese tertiary care hospitals, while the second used data from a Japanese administrative dataset. The study found a significant reduction in hospital mortality rates among patients who received early tapering of corticosteroids, specifically methylprednisolone at 1 g/day for 3 days followed by early tapering. The adjusted HR was 0.37 (95% CI 0.14 to 0.99) for the multi-centre cohort and 0.27 (95% CI 0.094 to 0.83) for the administrative cohort, indicating a lower risk of mortality in the early tapering group.

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Similarly, Cupero *et al*¹⁶ reported a higher dose of corticosteroids may increase hospital mortality rate; however, no significant association was found, with a HR of 1.31 (95% CI 0.26 to 6.55, $p=0.74$).

In contrast, Hyung *et al*¹⁸ reported improved hospital mortality rates with pulse corticosteroid therapy in patients with AE-IPF, with mortality rates of 18.6% for the pulse regimen versus 36.3% for the non-pulse regimen ($p=0.018$). The median daily dose of methylprednisolone in the first 3 days was 500 mg for the pulse group and 50 mg for the non-pulse group, highlighting substantial differences in corticosteroid administration between the two approaches.

Awano *et al*¹⁵ and Farrand *et al*¹⁷ found no significant difference in hospital mortality rate. Awano *et al*¹⁵ specifically compared in-hospital mortality rates in AE-IIP patients receiving high-dose versus low-dose corticosteroid therapy, revealing an OR of 0.86 (95% CI 0.64 to 1.16, $p=0.33$). Similarly, Farrand *et al*¹⁷ did not find a significant association between corticosteroid use and in-hospital mortality in AE-IPF patients, with an HR of 1.31 (95% CI 0.26 to 6.55, $p=0.74$), using a propensity score weighted, model. Lastly, Koshy *et al*²¹ reported a higher in-hospital mortality rate or lung transplantation in the corticosteroid group (34.8% vs 9.8%, OR 4.11, $p=0.049$).

28-day mortality

Awano *et al*¹⁵ also examined 28-day mortality rates, revealing no significant difference between high and low-dose corticosteroid groups. The OR for 28-day mortality in the low versus high-dose corticosteroid group was 0.88 (95% CI 0.64 to 1.23, $p=0.46$).

90-day mortality

Three studies investigated 90-day mortality with mixed results. Jang *et al*¹⁹ highlighted the efficacy of high-dose corticosteroids, demonstrating improved mortality outcomes (adjusted HR 0.221, 95% CI 0.102 to 0.480, $p<0.001$).

In contrast, Anan *et al*¹³ reported improved 90-day mortality with early tapering of corticosteroids, with adjusted HRs of 0.37 (95% CI 0.14 to 0.99), and 0.27 (95% CI 0.094 to 0.83), respectively.

Lastly, Hyung *et al*¹⁸ observed an 18% mortality risk reduction with pulse corticosteroids, but this was not statistically significant, with an adjusted of 0.82 (95% CI 0.50 to 1.37, $p=0.456$).

1-year mortality

Two studies examined 1-year mortality, with conflicting findings. Cuerpo *et al*¹⁶ reported that high-dose corticosteroids increased mortality, with an OR of 1.075 (95% CI 1.044 to 1.107, $p<0.001$). In contrast, Hyung *et al*¹⁸ found no difference in mortality between high and low-dose corticosteroid use with a HR of 0.89 (95% CI 0.60 to 1.33, $p=0.580$).

30-day rehospitalisation

Farrand *et al*¹⁷ reported no significant difference in 30-day rehospitalisation rates between patients who continued on corticosteroids after discharge and those who did not, with an adjusted HR of 1.81 (95% CI 0.46 to 7.17, $p=0.40$). Similarly, Koshy *et al*²¹ reported a 30-day readmission rate of 17% in the corticosteroid group versus 21% in the no-corticosteroid group, with an OR of 1.94 (95% CI 0.41 to 9.13, $p=0.40$).

Recurrent exacerbation

Yamazaki *et al*²⁰ found that higher total doses of corticosteroids within the first 1 to 30 days were associated with a lower risk of

exacerbation recurrence, with an adjusted HR of 0.61 (95% CI 0.41 to 0.90, $p=0.02$). Patients with IPF who did not experience recurrence of AE in the initial 1 to 30 days postdiagnosis received significantly higher total corticosteroid doses (5185 ± 2414 mg/month, 93.5 ± 44.0 mg/kg/month) compared with those with recurrence (3133 ± 1990 mg/month, 57.2 ± 37.7 mg/kg/month). However, no significant differences in total corticosteroid dose were observed for subsequent periods (31 to 60, 61 to 90, 91 to 120 and 151 to 180 post-AE). Among 63 patients discharged alive after their first AE-IPF, 14.3% experienced recurrence within a mean time of 233 ± 103 days, though recurrence criteria were not clearly defined.

We did not pursue a meta-analysis due to substantial differences across studies, such as varied AE-ILD definitions, differing corticosteroid protocols, inconsistent outcome measures and heterogeneous ILD populations. These variations present considerable challenges in generating reliable pooled estimates.

DISCUSSION

Summary of main findings

Our systematic review provides the first comprehensive analysis of corticosteroid therapy outcomes in acute exacerbations of interstitial lung disease (AE-ILD). Through synthesising data from nine studies, we offer a structured evaluation of corticosteroid therapy's impact on survival, rehospitalisation and recurrence rates across various ILD subtypes. Our primary aim was to assess the efficacy of corticosteroid therapy in AE-ILD, with a focus on survival time, 30-day rehospitalisation, exacerbation recurrence and mortality rates at specific intervals. This review also explores the influence of steroid dose and duration on these outcomes, identifies key limitations in existing data and suggests directions for future research.

KEY NOVEL FINDINGS AND CLINICAL IMPLICATIONS

Differential response patterns

Our analysis identifies novel patterns in treatment responses between IPF and non-IPF patients experiencing AE-ILD. Although individual studies have shown variable outcomes, our systematic approach reveals that high-dose corticosteroids may improve survival specifically in non-IPF patients with AE, whereas their effectiveness in AE-IPF remains uncertain. This finding provides a new evidence-based foundation for differentiating treatment approaches by ILD subtype.

Dose-response relationships

This review is the first to systematically assess the impact of corticosteroid dosing on multiple outcome measures. We found that higher cumulative corticosteroid doses within the first 30 days were associated with a lower risk of AE recurrence, though they did not significantly affect 30-day rehospitalisation rates.

Implications of treatment duration

Our analysis highlights distinct implications of acute versus chronic corticosteroid use. While high-dose short-term corticosteroid therapy may benefit certain patients during acute exacerbations, prolonged use, especially in IPF patients, may be unwarranted and potentially harmful. Study outcomes varied, with some indicating improved survival with higher doses, particularly in non-IPF ILD, while others showed no clear survival benefit. Hospital mortality rates also presented mixed evidence on the efficacy of high- versus low-dose regimens. Notably, higher cumulative corticosteroid doses in the initial 30

days correlated with a lower risk of AE recurrence, while rehospitalisation rates remained similar across dosing levels.

Selection biases in critically ill populations

Corticosteroid use in critically ill patients is often subject to selection bias due to the high risk of poor outcomes associated with severe illness. This makes it difficult to determine whether poor outcomes are due to ineffective treatment or the severity of the disease itself. Conversely, less severely ill patients who recover without corticosteroids might lead to perceptions of ineffectiveness or harm, while those who recover with corticosteroids may suggest potential benefits. Thus, corticosteroids may not be universally beneficial or harmful; their effectiveness is likely influenced by disease severity, ILD subtype and comorbidities. Additionally, concerns about adverse effects like immunosuppression and hyperglycaemia further complicate the assessment of high-dose corticosteroids in the acute management of AE-ILD.

Long-term corticosteroid use and maintenance therapy

Prolonged high-dose corticosteroids in stable patients, particularly in IPF, are likely unwarranted and potentially harmful. While corticosteroids can suppress inflammation²⁴ and attenuate acute lung injury,²⁵ their long-term use is associated with significant adverse effects and is not recommended for routine IPF management.²⁶ For non-IPF ILDs, corticosteroid use should be individualised based on specific disease characteristics and patient factors. There is a lack of studies on maintenance corticosteroids or steroid-sparing agents for reducing or preventing acute exacerbations in non-IPF patients, highlighting the need for further research into targeted therapies that effectively manage ILDs while minimising adverse effects.²⁷

Survival discrepancies and disease-specific responses

The discrepancy in survival after AE between non-IPF and IPF patients warrants careful consideration. While high-dose corticosteroids may provide survival benefits in non-IPF patients presenting with AE, their efficacy in AE-IPF remains uncertain. This disparity may reflect differences in disease pathophysiology, underlying inflammatory profiles or patient characteristics,^{4 28} highlighting the need for further research to elucidate factors associated with corticosteroid responsiveness in different ILD subtypes.

Re-evaluation of corticosteroid use in idiopathic pulmonary fibrosis (IPF)

The absence of a survival benefit from high-dose corticosteroid therapy in IPF indicates the need for cautious treatment planning. Long-term low-dose therapy has also proven ineffective in.⁴ For instance, Raghu *et al*²⁹ found no significant difference in mortality between IPF patients treated with high-dose prednisone, azathioprine and N-acetylcysteine versus placebo, prompting a re-evaluation of corticosteroid use in IPF management.²⁹

Strengths and limitations

Strengths of our systematic review include the use of four comprehensive search databases to identify potentially relevant articles and employing a formal review process to evaluate the eligibility of included articles based on predetermined criteria. This approach ensured that included studies provided sufficient information on definitions of ILD and AE-ILD, dose and duration of corticosteroid therapy, and outcomes of interest. The

review also provides detailed participant characteristics, aiding in risk assessment and stratification.

However, several limitations are present. First, the source studies did not consistently report causes of death, which limits the ability to fully assess the effect of corticosteroid therapy on survival outcomes. Second, the lack of severity comparison data between first and subsequent exacerbations hinders our understanding of how exacerbation severity may influence treatment response, particularly in recurrent cases. Third, the exclusion of non-English language articles may have led to study selection bias. Fourth, the inclusion of only observational studies and the lack of RCT evidence on this subject limit the ability to establish causation or fully interpret treatment impact. Fifth, included studies did not consistently differentiate between idiopathic and triggered exacerbations (such as infection, aspiration or drug-induced), which could significantly impact treatment response and outcomes. Sixth, included studies did not consistently adjust for potential confounders, including the baseline treatment for ILD, such as immunosuppressive medications, which are crucial in evaluating the response (or lack thereof) to corticosteroid therapy in AE-ILD and may impact the generalisability of their findings. Finally, the heterogeneity in the ILD subtype, definitions of AE-ILD, and variations in corticosteroid dosing regimens and treatment durations contribute to variability in the results.

FUTURE DIRECTIONS AND RECOMMENDATIONS

Future research efforts should concentrate on optimising corticosteroid therapy for AE-ILD by addressing several pivotal areas. Conducting randomised controlled trials to compare corticosteroid regimens is essential for defining optimal treatment protocols. Additionally, developing standardised AE-ILD definitions and consistent outcome measures would greatly enhance cross-study comparability. Critical investigation of treatment responses in idiopathic versus triggered exacerbations (including infection, aspiration or drug-induced causes) is needed to develop targeted therapeutic approaches for these distinct clinical scenarios. A more precise characterisation of patient populations and detailed analysis of specific mortality causes, including respiratory failure patterns, cardiovascular complications and infectious events, is equally important to deepen our understanding of treatment responses across diverse ILD subtypes. Prospective studies with predetermined protocols would yield more robust evidence to guide clinical decision-making. Further exploration into corticosteroid dosing strategies tailored to specific ILD subtypes, along with strategies to mitigate steroid-related complications, is crucial for maximising therapeutic efficacy while minimising adverse effects. Research should also focus on identifying predictive factors for different causes of death to enable more targeted therapeutic approaches. Collectively, these priorities aim to strengthen the foundation of AE-ILD management and improve patient outcomes.

In conclusion, our review highlights the complexity of corticosteroid therapy in ILD exacerbations and emphasises the importance of tailoring treatment approaches based on individual patient characteristics and disease subtypes. Notably, observed benefits, particularly reducing recurrence and improving survival, were associated with higher-dose corticosteroid regimens in some AE-ILD patients, particularly those with non-IPF disease. Further research is needed to develop additional treatment strategies, particularly in patients with IPF where therapeutic options are limited and morbidity appears greater.

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